Remarks

I. Addressing the Examiner's Rejection of Claims 6, 7, 11-13, 15, 17, 18 and 29 Under 35 U.S.C. §102(e).

The Examiner rejected claims 6, 7, 11-13, 15, 17, 18 and 29 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al. (U.S. Patent No. 6,080,578).

In the present application, independent claims 11 and 15 are pending. Following herein below, the applicants set forth their arguments that the cited reference does not anticipate the claimed invention at least with respect to the limitations present in the independent claims. Accordingly, the dependent claims define over the cited prior art at least by virtue of their inclusion of the limitations of the independent claims.

Applicants submit that the reference of Bischoff, et al., does not anticipate the claimed invention for all of applicants' previously submitted reasons of record, including, (1) that the reference of Bischoff, et al, does not teach all of the elements of the present invention; and (2) the presently claimed invention is not a natural result flowing from the disclosure of the Bischoff, et al., reference.

1. The reference of Bischoff, et al, does not teach all of the elements of the present invention.

Both of the pending independent method claims (i.e., claims 11 and 15) at least contain a limitation relating to preferential killing of dividing endothelial cells compared to quiescent endothelial cells by a replication competent adenovirus. The reference of Bischoff, et al., does not teach a method of killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a replication competent adenovirus. The reference of Bischoff, et al., makes no mention of endothelial cells. The reference of Bischoff, et al., makes no mention that replication competent adenovirus can provide preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. Further, the reference of Bischoff, et al., provides no teaching concerning mutant adenovirus replicating to higher titers in the dividing endothelial cells than wild type adenovirus (e.g., claim 11).

The reference of Bischoff, et al., teaches "(t)he mutant virus is able to substantially produce a replication phenotype in **neoplastic cells** but is substantially unable to produce a replication phenotype in non-replicating, non-neoplastic cells having essentially normal p53

and/or RB function" (see, e.g., Abstract of Bischoff, et al., emphasis added). Accordingly, the reference of Bischoff, et al., does not teach all of the elements of the claimed invention and cannot be said to anticipate the presently claimed invention.

The Examiner is relying on Bischoff, et al., to inherently teach the methods of the present invention. Such is obvious from the fact that the Examiner has not pointed to any teaching in the Bischoff, et al., reference concerning preferential killing of dividing endothelial cells compared to quiescent endothelial cells by a replication competent adenovirus. The Examiner's solution to this lack of teaching is to provide the following assertion:

> **It is noted** that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor, as well as non-dividing non-cancerous cells. **Therefore, administering the vector taught by Bischoff to a subject having a tumor would necessarily result** in substantially and selectively killing dividing endothelial cells (including dividing microvasculature) and cancer cells in the subject. (Emphasis added; Final Office action, dated 27 March 2007, pages 3-4.)

However, first, when an Examiner's rejection relies on inherency, it is incumbent on the Examiner to point to the page and line of the prior art that justifies the rejection. *See, e.g., Ex parte Schricker,* 56 USPQ2d 1723 (B.P.A.I. 2000) (unpublished). The Examiner has not so illustrated the basis in the reference for the Examiner's inherency argument.

Second, inherency is not present when prior art is only **capable** of being modified. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981)). The fact that a prior art reference is **capable** of being modified and the modification would anticipate the invention is not sufficient to support anticipation based on inherency. In *In re Robertson* (169 F.3d 743, 749 USPQ2d 1949 (Fed. Cir. 1999)), the Federal Circuit reversed an anticipation holding because

the prior art was only **capable** of being modified and one of ordinary skill would not have recognized such modification.

In the present application, a method of killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a replication competent adenovirus is NOT inherent in the method of Bischoff, et al., at least for the following reasons. Bischoff, et al., teaches "infecting the neoplastic cells with a recombinant adenovirus which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic cells. **The difference in replication phenotype of the adenovirus constructs of the invention in neoplastic and non-neoplastic cells provides a biological basis for viral-based therapy of cancer**" (see, Bischoff, et al., col. 3, lines 9-16; emphasis added). Even if one of ordinary skill in the art knows "that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor" (Final Office action, mailed 27 March 2007, pages 3-4) there is no reason to believe from the teachings Bischoff, et al., that treatment with a replication competent adenovirus would result in killing dividing endothelial cells with substantially less killing of quiescent cells. Accordingly, one of ordinary skill in the art would not have recognized the modification of the method of Bischoff, et al., suggested by the Examiner. Accordingly, the teaching relied upon by the Examiner for a determination of anticipation is NOT inherent in the reference of Bischoff, et al.

Regarding the teaching asserted by the Examiner to be inherent in the reference of Bischoff, et al., "such evidence must make clear that the missing descriptive matter is **necessarily** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268,20 U5PQ2d 1746, 1749 (Fed. Cir. 1991); emphasis added. In the present situation, it is NOT clear that the missing descriptive matter is present in the cited reference, NOR is it clear that it would so be recognized by one of ordinary skill in the art. Accordingly, the teaching relied upon by the Examiner for a determination of anticipation is NOT inherent in the reference of Bischoff, et al.

Third, the Federal Circuit has cautioned that all claimed elements must be found in the prior art for anticipation to be found:

> For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art .... Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there. *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997).

In the present case, the Examiner has presupposed the knowledge of one skilled in the art (i.e., "patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor," Final Office action, mailed 27 March 2007, pages 3-4); however, that presumed knowledge does NOT grant the Examiner a license to read into the reference of Bischoff, et al., teachings that are not there (e.g., a method of killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a replication competent adenovirus).

In the Examiner's response, the Examiner directly contradicts the Examiner's own statements with regard to the Examiner's assertion that the reference of Bischoff, et al., teaches all elements of the presently claimed invention:

> In response, it is noted that claimed method comprises steps that are identical to those of a method taught by Bischoff et al.; therefore, the same result would have been achieved in the prior art method. (Final Office action, mailed 27 March 2007, page 8.)

> Although Bischoff et al. is silent with respect to the limitations in the instant claims that the method would result in selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells, Bischoff et al. anticipates all of the claimed active method steps, so the function effects of the claimed methods are considered to be inherent in the method steps taught by Bischoff, et al. (Emphasis added; final Office action, mailed 27 March 2007, page 11).

As discussed herein above, the method steps of the presently claimed invention are NOT identical to the method steps taught by the reference of Bischoff, et al., for example, at least because the reference of Bischoff, et al., contains no teaching regarding selective killing of dividing endothelial cells. The Examiner acknowledges this point in the second paragraph cited above (i.e., the paragraph from page 11).

Further, the Examiner has only asserted and not supported that "the function effects

of the claimed methods are considered to be inherent in the method steps taught by Bischoff, et al." For the reasons discussed herein above, applicants submit that this teaching is NOT inherent in the reference of Bischoff, et al.

In view of the above-presented arguments, applicants submit that the Examiner has failed to establish a case of anticipation for the claimed invention. Further, the Examiner has failed to establish that the reasoning asserted by the Examiner as the basis for the rejection is inherent in the cited reference.

2. The presently claimed invention is not a natural result flowing from the disclosure of the Bischoff, et al., reference.

The Examiner's arguments asserting anticipation of the presently claimed invention by the teachings of the reference of Bischoff, et al., is essentially an argument that the methods of the present invention relating to preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, particularly microvascular endothelial cells, are inherent in the methods of preferential killing of neoplastic cells taught by the reference of Bischoff, et al.

In the absence of the teachings of the present specification, one of ordinary skill in the art would not be guided to use replication competent adenovirus to preferentially kill dividing endothelial cells relative to killing of quiescent endothelial cells, which in and of itself provides an art recognized cancer treatment (i.e., disruption of tumor angiogenesis) separable from direct killing of tumor cells (i.e., neoplastic cells).

The methods of the present invention, however, are directed to preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells, by a replication competent adenovirus. The endothelium comprises a single layer of flat cells that line the interior surface of blood vessels. The endothellium forms an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells are the cells that make up the inside of blood vessels. Angiogenesis is the formation of new blood vessels. Angiogenesis has come to be appreciated as a continuous and important process in tumor development, wherein a tumor may gain an independent blood supply. The process of angiogenesis is believed to be driven by the tumor releasing signals that induce angiogenesis, such as VEGF, by binding to

endothelial cell receptors near the tumor (see, e.g., Berse, B., et al., Molec. Cell. Biol. 1992 Feb;3(2):211-20); Warren, R.S., et al., J. Clin. Invest. 1995 Apr;95(4):1789-97). The control of tumor angiogensis has been toutcd as an **alternative** method of controlling tumor growth versus direct destruction of tumor cells.

The reference of Bischoff, et al., contains no teaching that would direct one of ordinary skill in the art to use the described adenoviral vectors as an alternative method of controlling tumor growth, that is, preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells. The reference of Bischoff, et al., teaches only the killing of neoplastic cells using recombinant adenovirus substantially replication deficient in non-neoplastic cells.

There is no anticipation when the prior art use is different. A holding of no anticipation may be found in instances where the general subject matter is the same, but the specific application or use is different. For example, in Union Oil Co. of California (Unocal) v. Atlantic Richfield Co. (Atlantic) (*Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000*), cert. denied,* 531 U.S. 1183 (2001)), the invention related to automotive gasoline compositions that reduced automobile tailpipe emissions (in the present case corresponds to -- a method of killing dividing endothelial cells with substantially less killing of quiescent endothelial cells by contacting the cells under infective conditions with a replication competent adenovirus).

In *Oil Co. of Cal. v. Atlantic Richfield Co.* the inventors sought to reduce the levels of carbon monoxide (GO), nitrous oxide (NOx), and hydrocarbons (HC) emitted from automobile tailpipes. After considerable experimentation, the inventors discovered relationships between the various petroleum characteristics described above and tailpipe emissions (in the present case corresponds to -- applicants demonstrated killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a replication competent adenovirus).

Atlantic originally sued Unocal in district court, seeking a declaratory judgment to invalidate the patent. Unocal counterclaimed, alleging willful infringement of the patent. The district court then construed the claims of the patent and limited the claims to automotive fuels. An appellate court requires that a party seeking to invalidate a patent under 35 U.S.C. §102 show that the allegedly invalidating prior art contains each and every element of the

claimed invention.

The district court emphasized that the claims of the patent recited either "[a]n unleaded gasoline suitable for combustion in an automotive engine" or '[a]n unleaded gasoline fuel suitable for combustion in a spark ignition automotive engine (in the present case this corresponds to -- the method claims are generally directed to a replication competent adenovirus that substantially, preferentially kill dividing endothelial cells, for example, microvascular endothelial cells). The court held that the claims were not anticipated by prior art aviation and racing fuel compositions that were alleged to be the same by Atlantic (in the present case this corresponds to -- the reference of Bischoff, et al., teaches the killing of neoplastic cells using recombinant adenovirus substantially replication deficient in non-neoplastic cells).

An appellate court reviews a finding of anticipation as a question of fact. Therefore, on appeal, an appellate court must affirm the district court's denial of a judgment as a matter of law on anticipation if substantial evidence supports the jury's verdict that the cited prior art did not anticipate the claims. On appeal, the Federal Circuit affirmed, reasoning as follows:

> Because the '393 patent [U.S. Patent 5,288,393] covered only standard automotive fuel, the district court correctly determined that specialty fuels within other limitations of the claims do not anticipate under 35 U.S.C. Section 102. In other words, the aviation and racing fuels that allegedly invalidate the '393 claims do not anticipate because they do not contain each and every limitation of the claims .... Specifically, this alleged prior art does not include the limitation of being a standard automotive fuel composition. Moreover, the record does not show that the aviation and racing fuels otherwise have the claimed characteristics of the particular standard automotive fuels recited in the '393 patent. While the record shows that some properties of the aviation and racing fuels coincide with the properties of the '393 patent's claims, the record does not show the presence of each and every limitation. (*Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000).)

Correspondingly, in the present case the method of killing of neoplastic cells using recombinant adenovirus substantially replication deficient in non-neoplastic cells as taught by Bischoff, et al., (in Unical v. Atlantic corresponds to -- "the aviation and racing fuels") that allegedly invalidate the claims directed to a method of preferential killing of dividing endothelial cells compared to quiescent endothelial cells by a replication competent adenovirus (in Unical v. Atlantic corresponds to -- "the '393 claims" related to automotive

fuel) do not anticipate because they do not contain each and every limitation of the claims.

Specifically, the reference of Bischoff, et al., (in Unical v. Atlantic corresponds to -- "the alleged prior art") does not include the limitation of substantially, preferentially killing dividing endothelial cells using a replication competent adenovirus (in Unical v. Atlantic corresponds to -- "being a standard automotive fuel composition"). Moreover, the record does not show that the target neoplastic cells of Bischoff, et al., (Unical v. Atlantic corresponds to -- "aviation and racing fuels") otherwise have the characteristics of the dividing endothelial cells of the methods of the present invention (Unical v. Atlantic corresponds to -- "particular standard automotive fuels recited in the '393 patent).

Accordingly, the Federal Circuit held that claims that cover only standard unleaded automotive gasoline (in the present case this corresponds to -- use of a replication competent adenovirus for substantially, preferential killing dividing endothelial cells, for example, microvascular endothelial cells) were not anticipated by aviation and racing fuels (in the present case this corresponds to -- the killing of neoplastic cells using recombinant adenovirus substantially replication deficient in non-neoplastic cells) because the prior art compositions did not include the limitation of being, or being applicable to, a standard automotive fuel (in the present case corresponds to -- the reference of Bischoff, et al., does not include the limitation of preferential killing of dividing endothelial cells, for example, microvascular endothelial cells using a replication competent adenovirus).

Therefore, the Federal Circuit held that the prior art racing and aviation fuels did not contain each and every limitation of the claims at issue and were therefore not anticipated. Correspondingly, in the present case, applicants submit that the cited reference of Bischoff, et al., does not contain each and every limitation of the claims at issue (e.g., use of a replication competent adenovirus for substantially, preferentially killing dividing endothelial cells, for example, microvascular endothelial cells) and the present claims are therefore NOT anticipated.

There is no teaching in the reference of Bischoff, et al., that would guide one of ordinary skill in the art to use the methods of the present invention to achieve the result of the present invention, that is, a method for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. For example, in a situation where a target tumor did not respond to direct killing of neoplastic cells by a selected method (e.g.,

chemotherapy), in view of the teachings of the present specification one of ordinary skill in the art may choose an alternative method to target the dividing endothelial cells to reduce or eliminate angiogenesis which provides a blood supply to a tumor. The teachings of Bischoff, et al., would not direct one of ordinary skill in the art to such an approach. Accordingly, the teachings of the reference of Bischoff, et al., do not anticipate the claimed invention.

Accordingly, in view of the above arguments, applicants submit that the reference of Bischoff, et al., does not provide teachings that anticipate the presently claimed invention. Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §102(e).

II. Addressing the Examiner's Rejection of Claims 22 and 23 Under 35 U.S.C. §102(b).

The Examiner rejected claim 22 under 35 U.S.C. §102(b) asserting that the claims are anticipated by Whyte, et al. (J. Virol. 1988, previously of record).

The Examiner rejected claim 23 under 35 U.S.C. §102(b) asserting that the claims are anticipated by Jelsma, et al., (Virol. 1989, previously of record).

In this paper, applicants cancel claims 22 and 23. Cancellation of claims 22 and 23 obviates the rejection of these claims.

III. Addressing the Examiner's Rejection of Claims 6-13, 15, 17-20, 22, 23, and 26-34 under 35 U.S.C. §112, First Paragraph.

The Examiner rejected claims 6-13, 15, 17-20, 22, 23, and 26-34 under 35 U.S.C. §112, first paragraph, asserting that the specification, "while being enabling for: methods of selectively killing dividing cells in a population of dividing and quiescent cells by administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region directly to the target dividing cells, does not reasonably provide enablement for the full scope of the claims." (Office action, dated 12 July 2006, page 5, emphasis in original.)

For the reasons of record, applicants submit that the Examiner has failed to establish a *prima facie* case for lack of enablement commensurate in scope with these claims. Further, for reasons of record applicants submit that the specification provides enablement commensurate in scope with the claimed subject matter. However, in an effort to facilitate

prosecution and to place the claims in better condition for appeal, applicants have amended independent claims 11 and 15 to include the limitation that administration of the replication competent adenovirus is achieved by direct administration of the replication competent adenovirus to the target cell population.

As noted by the Examiner:

> Claims 6-13, 15, 17-20 and 29-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: methods of treatment comprising administering a replication competent adenovirus comprising a mutation in an EIA CR2 RB family member binding region directly to the target cells, does not reasonably provide enablement for the full scope of the claims. (Bold emphasis added, underlined emphasis in the original; final Office action, mailed 27 March 2007, page 14).
>
> With respect to the rejection of claims 6-13, 15, 17-20 and 29-34 under 35 U.S.C. 112, first paragraph, it is respectfully pointed out that **the only issue remaining is the route of administration.** (Bold emphasis added; final Office action, mailed 27 March 2007, page 5).
>
> Applicants argue that the specification teaches a variety of formulations and methods of administration for the vector for use in the claimed methods and refer to the specification on pages 13-15. In addition, applicants refer to U.S. Patent No. 5,677,178 incorporated by reference in its entirety, which indicates that an adenovirus suspension may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladder cancer).
>
> In response, **it is noted that all of these administrations appear be administrations that directly deliver the vector to the target tissue.** (Bold emphasis added; final Office action, mailed 27 March 2007, pages 15-16).

37 C.F.R. §1.116, "Amendments and affidavits or other evidence after final action and prior to appeal," states that "(1) An amendment may be made canceling claims or complying with any requirement of form expressly set forth in a previous Office action; (2) An amendment presenting rejected claims in better form for consideration on appeal may be

admitted." Further, MPEP §714.12 states: "Once a final rejection that is not premature has been entered in an application, applicant or patent owner no longer has any right to unrestricted further prosecution. This does not mean that no further amendment or argument will be considered. Any amendment that will place the application either in condition for allowance or in better form for appeal may be entered."

Applicants respectfully request entry of the amendments to claims 11 and 15 as entry of the amendments result in a claim set (i) consistent with the requirement for enablement as identified by the Examiner, and (ii) will reduce the number of issues for appeal, thus placing the application in better form for appeal.

By these amendments to the pending independent method claims 11 and 15, the limitations introduced into the independent claims obviate the enablement rejection of the dependent claims thereon.

In view of the above amendments, applicants submit that the claims comply with scope of enablement for the claims that was indicated as enabled by the Examiner. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502 or the undersigned at (650) 780-9030.

Respectfully submitted,

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